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ORIGINAL ARTICLE

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Aims: To assess the value of a near-patient brain natriuretic peptide (BNP) test to predict medium term (3 month) serious outcome for adult syncope patients presenting to a UK emergency department (ED).
Methods: This was a prospective cohort pilot study. Consecutive patients aged ⩾16 years presenting with syncope over a 3 month period were eligible for prospective enrolment. All patients who were medium or high risk according to our ED's existing syncope guidelines underwent near-patient BNP testing using the Triage point of care machine.
Results: 99 patients were recruited. 72 of 82 high and medium risk patients underwent BNP measurement. 11 patients had a serious outcome, 9 of whom had BNP measured. In 25 (35%) patients, BNP was ⩾100 pg/ml, and in 3 of these it was >1000 pg/ml. 6 of the 25 patients (24%) with a BNP >100 pg/ml, and all 3 patients with a BNP >1000 pg/ml, were in the serious outcome group. BNP was raised over 100 pg/ml in 6 of the 9 serious outcome patients having a BNP measured (66%), and over 1000 pg/ml in 3 (33%).
Conclusions: This early work suggests that BNP may have a role in the risk assessment of syncope patients in the ED. Further work is required to see how BNP interacts with other clinical variables. Near-patient BNP testing may be shown to be an independent predictor of adverse outcome either alone or incorporated into existing syncope clinical decision rules and scores in order to improve their sensitivity and specificity. Further studies are required to evaluate this.

Syncope is a transient, self limited loss of consciousness usually leading to falling.[1] It accounts for 3% of emergency department (ED) visits and 1–6% of hospital medical admissions, affecting 6 per 1000 people per year.[2 3] In 1983, Kapoor *et al*[4] published the first prospective syncope study showing a 12 month mortality of 14%. Mortality was greatest in patients in whom a cardiovascular cause was identified (30%). Subsequent studies have shown that underlying heart disease in patients with syncope is associated with a poor prognosis.[5]

Recent emphasis has focused on risk stratifying syncope patients. With growing pressures on acute medical beds and an increasingly elderly population, there is a need to identify high risk populations requiring further investigation, and low risk patients who may be discharged safely. Accurate identification of such groups would enable specific targeting of resources and prevent excessive investigation of patients with benign causes of syncope. No risk stratification studies have yet investigated the role of biochemical markers in risk stratification.

Brain (or B-type) natriuretic peptide (BNP), which is secreted in response to an increase in ventricular volume and pressure load, is known to be an excellent marker of prognosis in patients with heart failure or cardiac disease.[6 7] As previously mentioned, it is well established that prognosis in syncope is related to the presence of underlying heart disease,[5] and all existing syncope clinical decision rules include either a history of congestive heart failure[8–11] or of underlying cardiac disease.[12 13] Tanimoto *et al* in 2004 conducted the only syncope study to date that has utilised BNP.[14] This study evaluated the usefulness of BNP to separate cardiac and non-cardiac causes of syncope. The investigators retrospectively evaluated 148 consecutive syncope patients admitted to hospital; 61 of these patients were found to have a cardiac cause for their syncope. A BNP value of ⩾40 pg/ml was found to be 82% sensitive and 92% specific for identifying cardiac syncope.

We therefore hypothesised that BNP could be an excellent ED marker of medium term (3 month) syncope outcome. The aim of this pilot study was to assess the value of a near-patient BNP test to predict medium term (3 month) serious outcome for syncope patients presenting to a UK ED, and to compare the performance of BNP with our existing departmental syncope guidelines (table 1) based on the European Society of Cardiology,[1 15] the American College of Physicians,[16 17] and the American College of Emergency Physicians guidelines.[18]

METHODS

Setting

The ED of the Royal Infirmary of Edinburgh (85 000 adult attendances per annum).

Inclusion criteria

Consecutive patients presenting with syncope aged 16 years or over between 7 November 2005 and 7 February 2006 were eligible for prospective enrolment. Syncope was defined as a transient loss of consciousness with an inability to maintain postural tone, followed by a spontaneous recovery without need for therapeutic or electrical intervention. Data from this same patient cohort were used to compare our existing ED guidelines with the San Francisco Syncope Rule[10 11] and the OESIL score,[13] and has been published previously.[19]

Exclusion criteria

Patients under 16 years of age, those previously recruited, and those having a history of seizure with prolonged post-ictal phase were excluded. Patients who were unable to give either written or verbal informed consent were also excluded.

Abbreviations: BNP, brain natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; ED, emergency department; EPR, electronic patient records; IQR, interquartile range

Table 1 Our existing emergency department syncope guidelines based on the European Society of Cardiology,[1 15] the American College of Physicians,[16 17] and the American College of Emergency Physicians guidelines[18]

High risk (admit)	Medium risk (consider discharge with early outpatient review)
History findings ● Palpitations related to syncope ● Associated chest pain ● Associated headache ● Related to exertion ● Family history of sudden death <60 ● Previous history of VT/VF/cardiac arrest	*History findings* ● Age >60 years ● No prodromal symptoms ● Previous myocardial infarct ● Known history of valvular heart disease ● Known angina/coronary artery disease ● Known history of congestive cardiac failure
Examination findings ● Systolic heart murmur heard ● Signs of heart failure present ● Systolic BP <90 mm Hg ● Suspicion of pulmonary embolism ● AAA detected ● New neurological signs on examination ● Suspicion of CVA or SAH ● FOB present on PR exam ● Other suspicions of GI bleed	*Examination findings* ● >20 mm Hg drop on standing ● Diastolic heart murmur heard ● Ventricular pause >3 s on carotid sinus massage ● Trauma associated with collapse
ECG findings ● Mobitz type II second degree heart block ● Mobitz type I (aka Wenkebach) second degree heart block ● Bifascicular block ● Complete heart block ● Sinus pause >3 s ● New ST elevation ● VT ● Sinus bradycardia <50 ● Sinoatrial block ● QTc >450 ms ● New T wave/ST segment changes ● Brugada syndrome (ST segment elevation V1–V3) ● Arrhythmogenic right ventricular dysplasia	*ECG findings* ● Right bundle branch block ● QRS duration >120 ms ● Old T wave/ST segment changes ● Frequent pre-excited QRS complexes ● Q waves unchanged from old ECG ● Atrial fibrillation or flutter ● PR >200 ms (1st degree heart block)
	Low risk (consider discharge) ● None of the above characteristics

AAA, abdominal aortic aneurysm; BP, blood pressure; CVA, cerebrovascular accident; ECG, electrocardiogram; FOB, faecal occult blood; GI, gastrointestinal; PR, per rectum; SAH, subarachnoid haemorrhage; VF, ventricular fibrillation; VT, ventricular tachycardia.

Study enrolment

Eligible patients were flagged at the ED high dependency triage area and a data collection form was placed in the patient's records. The treating doctor was responsible for deciding eligibility. Assessment of patients was carried out by routine ED clinical staff. A decision to enrol a patient was not overturned later by the study team and enrolled patients were analysed on an intention to treat basis. Written consent was obtained from all enrolled patients. This study received ethical approval from Lothian's Regional Ethical Committee.

Assessment

All patients underwent a standardised assessment using 31 predetermined variables (11 focused on clinical features, 9 on past medical history, and 11 concerning current medication), 28 examination variables and 26 electrocardiogram (ECG) variables. After a full history and examination, all patients who were medium or high risk according to our ED's existing syncope guidelines also had near-patient BNP testing. BNP was measured using a whole blood immunoassay technique utilising the Triage point of care machine. Treating physicians were not blinded to the result of the BNP test. Admitted patients also underwent a laboratory based troponin I at least 12 h post-syncope at the discretion of the admitting team. Patients were admitted, referred to medical outpatients, or discharged according to our ED's existing syncope guidelines and a study data collection form was completed for each patient.

End point measures

The primary end point was serious outcome at 3 months. Serious outcomes were pre-defined and were all cause death, acute myocardial infarction (history of chest pain or ECG changes and troponin I >2.0), life threatening arrhythmia (documented on monitor or ECG during inpatient stay or on outpatient Holter monitoring, and requiring treatment), pulmonary embolus (confirmed on ventilation perfusion scan (VQ) or CT pulmonary angiography scan (CTPA), and requiring treatment), cerebrovascular accident/subarachnoid haemorrhage (CT or lumbar puncture diagnosis), haemorrhage requiring a blood transfusion of 2 units or more during inpatient stay, and an acute surgical procedure or endoscopic intervention secondary to a suspected cause of syncope.

Once 3 months had elapsed following ED attendance, the hospital computer system was interrogated to see whether each patient had returned to any hospital in the Lothian region. The hospital records were reviewed for all patients who had attended the ED or outpatient department or who had been admitted as an inpatient. Any deceased patient in the Lothian region was also able to be identified via the hospital computer system and hospital records were acquired.

Hospital notes were reviewed to determine whether each patient had had a serious outcome within 3 months of their attendance to the ED with syncope. All patients were followed up. Two recruited patients from outside Lothian were contacted by phone. Hospital notes were available for all patients.

Table 2 Description of the 11 patients with a serious outcome

Patient study no.	Age	Sex	Serious outcome	Patient ESC risk	BNP pg/ml
7	68	M	Extreme bradycardia on 24 h tape including 2 pauses of 3.5 s and 4.0 s. Permanent pacemaker inserted. Alive at 3 months	Medium	461
17	71	M	Had AAA repair on day 1 with good recovery. Presented to the ED day 80 with leaking AAA repair. Died in theatre	High	–
24	90	F	Myocardial infarction (troponin 14.40). Also fast AF. Alive at 3 months	High	1340
32	67	M	Re-presented to the emergency department in cardiac arrest day 32. Unsuccessfully resuscitated. Primary cause unknown	High	2040
43	91	M	Ventricular standstill on ward. Permanent pacemaker inserted. Alive at 3 months	High	82.5
52	66	M	Died in hospital on day 79 after a hospital readmission. Cause not identified	High	26.5
55	76	M	Multiple episodes of ventricular tachycardia on ward. Internal defibrillator implanted. Alive at 3 months	High	–
59	76	M	2 episodes of ventricular standstill 7 s and 5 s each on 24 h tape. Diagnosis of episodic complete heart block made and permanent pacemaker inserted. Alive at 3 months	Medium	16.3
63	57	F	Died day 6 after index hospital admission. Syncope secondary to massive upper gastrointestinal haemorrhage. Patient also had terminal lung cancer	High	1040
66	74	M	Died day 6 after index hospital admission of left internal carotid artery thrombosis and left cerebral infarct. Also secondary right sided bronchopneumonia	Medium	144
78	81	F	Initial syncope thought secondary to hypotension. Interval 24 h tape showed episodes of fast AF and 5 prolonged pauses up to 3.6 s. Permanent pacemaker inserted. Alive at 3 months	Medium	489

AAA, abdominal aortic aneurysm; AF, atrial fibrillation; BNP, brain natriuretic peptide; ED, emergency department; ESC, European Society of Cardiology; F, female; M, male.

Review of missed patients

In order to determine the recruitment rate of patients into the study, a retrospective search was conducted of all ED electronic patient records (EPR) between 7 November 2005 and 7 February 2006 looking for the keywords ''syncope'', ''collapse'', ''faint'', ''loss of consciousness'' or ''loc'' appearing anywhere on the EPR. All EPRs with one of these terms were then hand searched and a decision was made from the notes whether the patient fitted the study's inclusion criteria. A list was compiled of all patients who fitted the study inclusion criteria but who had not been enrolled, along with their demographic details, and these were compared to those patients who had been enrolled into the study.

Statistical analysis

All patient data were entered into a specially designed Microsoft Access database and exported into Microsoft Excel for statistical analysis. Sensitivity, specificity, predictive values and likelihood ratios were calculated for BNP >100 pg/ml, BNP >1000 pg/ml and for current ED guidelines, and serious and non-serious outcome groups were compared using the Fisher exact test. The small sample size precluded calculation of receiver operator curves. The BNP cut off values of 100 pg/ml and 1000 pg/ml were decided before the study. The Triage point of care BNP assay defines any BNP value >100 pg/ml as an abnormal value. This value and a value 10-fold greater were arbitrarily chosen for analysis. This upper cut off was chosen as it was thought to be potentially high enough to be a possible rule-in value. A future larger study will attempt to define possible rule-in and rule-out levels using receiver operator curves.

The ''study group'' and the ''missed group'' were compared using the χ^2 test and the Mann–Whitney U test, and the ''BNP group'' and the ''missed BNP'' group were compared using the Fisher exact test.

RESULTS

Ninety-nine consecutive adult patients were recruited over a 3 month period between 7 November 2005 and 7 February 2006. It was thought that 100 patients had been enrolled; however, one patient episode had been erroneously duplicated

Table 3 Summary of results

	Serious outcome	No serious outcome	Total
Total patients	11 (11%)	88 (89%)	99
Admitted	11 (25%)	33 (75%)	44
Discharged	0 (0%)	55 (100%)	55
High risk group (based on ED guidelines)	7 (22%)	25 (78%)	32
Medium risk group (based on ED guidelines)	4 (8%)	47 (92%)	51
Low risk group (based on ED guidelines)	0 (0%)	16 (100%)	16
BNP not measured	2 (7%)	25 (93%)	27
BNP <100 pg/ml	3 (6%)	44 (94%)	47
BNP ⩾100 pg/ml but <1000 pg/ml	3 (14%)	19 (86%)	22
BNP ⩾1000 pg/ml	3 (100%)	0 (0%)	3

BNP, brain natriuretic peptide; ED, emergency department.

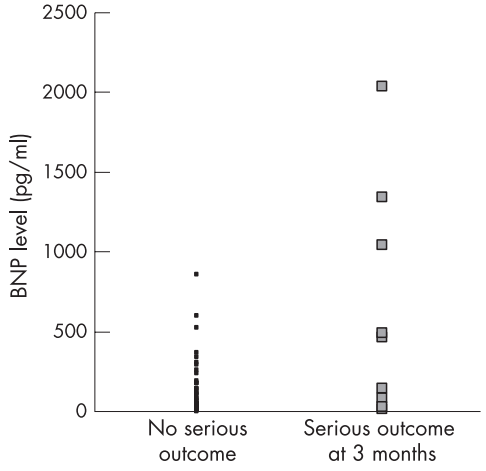

Figure 1 Relation between brain natriuretic peptide (BNP) level and outcome of study patients at 3 months.

during data entry. Forty-four patients were admitted to hospital and 55 were discharged from the ED. Eight of the 11 patients with a serious outcome had this by 7 days, and three further patients had developed a serious outcome by 3 months. In total, therefore, 11 patients (11.1%) had a serious outcome by 3 months. Of these, five patients had died and six others had an alternative serious outcome (table 2). All 11 had been admitted to hospital from the ED (table 3).

Seventy-two of the 82 medium and high risk patients had BNP measured, nine of whom had a serious outcome (12.5%) (fig 1). Those medium and high risk patients who did not undergo BNP measurement were missed because of either enrolling doctor error (seven patients) or BNP Triage point of care machine or operator error (three patients). The percentage serious outcome in those high and medium risk patients having BNP measured (72 patients) and the percentage serious outcome in the high and medium risk patients who did have BNP measured (10 patients) was not significantly different ($p = 0.617$, ns, Fisher exact test).

A BNP cut off of ⩾100 pg/ml was more sensitive than current ED guidelines for predicting medium term (3 month) serious outcome for syncope patients presenting to our ED (0.667 vs 0.636) with a similar specificity (table 4). A BNP cut off of ⩾1000 pg/ml had a specificity of 1 compared to that of 0.716 for current ED guidelines. While the BNP in two of these patients would have been unlikely to affect a decision to admit (acute myocardial infarction and massive upper gastrointestinal bleed both apparent on admission), in the third, there was no suspicion of likely poor outcome at the time of the patient's initial presentation to the ED.

Thirty of those admitted had troponin I measured, and only one of these was raised (14.40 ng/ml). This was thought to be due to an acute myocardial infarction. Of the 11 patients who developed a serious outcome, six had troponin measured and in only one was it raised.

A total of 263 patients presenting during the study period were identified from the EPR search as fitting the study's inclusion criteria. The study therefore enrolled 37.6% of patients eligible for inclusion. There were 74 men (45%) and 90 women in the ''missed group'', compared to 48 men (48%) and 51 women in the ''study group'' ($p = 0.60$, ns, χ^2). Neither the ages of the ''study group'' or ''missed group'' were normally distributed. Median age of the ''study group'' was 71.0 years (interquartile range (IQR) 47–81 years) and of the ''missed group'' was 62.5 years (IQR 29–78 years) ($p = 0.047$, significant at the 5% level, Mann–Whitney U test).

Table 4 Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and p value of selected characteristics

	PPV	NPV	Sensitivity	Specificity	+LR	−LR
BNP >100 pg/ml	0.240 (0.102 to 0.455)	0.936 (0.814 to 0.983)	0.667 (0.309 to 0.910)	0.698 (0.568 to 0.804)	2.211 (1.219 to 4.010)	0.477 (0.187 to 1.219)
BNP >1000 pg/ml	1.000 (0.310 to 1.000)	0.913 (0.814 to 0.964)	0.333 (0.090 to 0.691)	1.000 (0.928 to 1.000)	Inf (n/a)	0.667 (0.420 to 1.058)
High risk group (based on ED guidelines)	0.219 (0.099 to 0.404)	0.940 (0.847 to 0.981)	0.636 (0.316 to 0.876)	0.716 (0.608 to 0.804)	2.240 (1.284 to 3.907)	0.508 (0.230 to 1.120)

BNP, brain natriuretic peptide; ED, emergency department; +LR, positive likelihood ratio; −LR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value. Confidence intervals in parentheses.

DISCUSSION

This is the first study that has looked at using biochemical markers to aid rapid risk stratification of patients presenting to the ED with syncope. There are currently several risk stratification scores[8–13] and also various guidelines to help the emergency physician decide who should be admitted for further investigation, and who could be safely discharged. Some of these rules have been derived to predict short term outcome (7 days) and some to predict longer term outcome (12 months).

We chose to look at a medium term (3 month) serious outcome. The goal of an ED risk stratification tool is to detect patients who are at risk of an imminent serious outcome, the course of which may be altered by early investigation, admission and intervention. A proportion of the short term (7 day) serious outcomes were expected to include such conditions as ruptured abdominal aortic aneurysms and subarachnoid haemorrhages. BNP is unlikely to be useful at predicting serious outcome in this non-cardiac syncope group. We also decided not to measure BNP in patients who were classified as low risk. This was because of the expected very low rate of serious outcome in this group.

Only one patient who had an adverse outcome had a raised troponin I at 12 h. This suggests that the good sensitivity that BNP shows for serious outcome is not due to it acting as a marker of myocardial ischaemia.

Patients who had been ''missed'' for inclusion into the study were statistically slightly younger compared to those enrolled into the ''study'' group. This is probably due to ED staff failing to enrol some younger syncope patients into the study. These patients would be more likely to be low risk and would therefore not have been eligible for BNP and troponin I testing. This difference is therefore unlikely to have biased the study findings.

This study shows that BNP may be a very useful predictor of serious outcome in syncope patients presenting to the ED. The advantage of the near-patient test is its immediate availability which makes it extremely useful for rapid ED decision making. BNP should now be included as a predictor variable in a large derivation and validation study of syncope to see if it is an independent predictor of adverse outcome and, if so, whether it has a role alone or as part of a clinical decision rule to aid the management of patients presenting with possible cardiac syncope to the ED. A power calculation suggests that 500 patients would be required in both the derivation and validation arms of such a study.

Conclusions

This early work suggests that BNP may have a role in the risk assessment of syncope patients in the ED. Further work is required to see how BNP interacts with other clinical variables. A BNP cut off of $\geqslant$100 pg/ml has a reasonable sensitivity for serious outcome, while a cut off of $\geqslant$1000 pg/ml has an excellent positive predictive value and specificity. Near-patient BNP testing may be shown to be an independent predictor of adverse outcome either alone or incorporated into existing syncope clinical decision rules and scores in order to improve their sensitivity and specificity. Further studies are required to evaluate this.

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